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Continuous opioid substitution treatment over five years: heroin use trajectories and outcomes

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Abstract

Background: This is the first national study in England of continuous long-term opioid substitution treatment (OST).

Methods: All adults admitted to community OST for opioid use disorder (OUD) in 2008/09, with continuous enrolment to 2013/14 (n=7,719). Heroin use trajectories were identified by multilevel Latent Class Growth Analysis. In Year 6 and 7 of follow-up, the outcome measure (analysed by multilevel, multivariable logistic regression) was 'successful completion and no re-presentation' (SCNR) to community treatment within six months.

Results: Five heroin use trajectory classes were identified: '*gradual decreasing'* (20.9%); '*decreasing then increasing'* (21.7%); '*continued low-level'* (17.0%); '*rapid decreasing'* (25.6%), and '*continued high-level'* (14.8%). At the end of Year 7, 4,616 people (60.3%) remained in OST. Of those discharged, 28.8% achieved the SCNR follow-up outcome. SCNR was more likely in the '*gradual decreasing'* (adjusted odds ratio [AOR] 2.40; 95% confidence interval [CI] 1.77-3.26), '*continued low-level'* (AOR 2.46; CI 1.78-3.40) and '*rapid decreasing'* (AOR 3.40; CI 2.43-4.37) classes, relative to the '*continued high-level'* class. SCNR was more likely among patients employed at admission (AOR 1.45; 95% CI 1.15 to 1.83) and those receiving adjunctive psychosocial interventions (AOR 1.44; 95% CI 1.03 to 2.02).

Conclusions: Among English patients in OST for 5-years, heroin use trajectories were clearly delineated, with a gradient of response on the study outcome. Successful completion and no re-presentation was achieved by 28.8% of discharged patients. The rapid decreasing trajectory had the greatest likelihood of outcome. Adjunctive psychosocial intervention during OST was associated with positive outcome.

Keywords: Treatment effectiveness; opioid use disorder; national; developmental trajectory

1. Introduction

Oral methadone or buprenorphine are the first-line medical therapies for opioid use disorder (OUD). These opioid substitution treatments (OST) are consistently associated with abstinence from illicit opioid use (e.g. Hubbard et al., 2003; Gossop et al., 2003; Teesson et al., 2006), a lower risk of opioid overdose (White et al., 2015), and reductions in criminal behaviour (Gossop et al., 2005). Aggregate statistical results may, however, mask differential clinical response among sub-populations. For example, in an English national study of ongoing OUD treatment, 37% of patients were abstaining from heroin during the 28-days before six-month follow-up; a further 31% were using heroin less often; but 29% continued to use heroin at the same frequency as at admission, and 3% had deteriorated (Marsden et al., 2009).

Longer follow-up studies have identified distinct sub-populations of people who share a similar heroin use trajectory. In a US cohort study of 471 heroin users followed-up over 16 years, Hser and colleagues identified three classes: nine per cent were 'early-quitters'; 32% achieved improvements at a later stage in follow-up ('late-decelerated users'), and 59% were labelled 'stably high-level' heroin users with no identifiable improvement (Hser et al., 2007). In a recent 4.5 year follow-up of study of 795 participants in a treatment trial, Hser's group identified the following classes: 'low use' (42.0%); 'high use' (22.3%); 'decreasing use' (18.6%); and 'increasing use' (17.1%), with people in the 'decreasing use' class spending more time in treatment than those in the 'high use' class (Hser et al., 2017). Comparable findings have been reported in Australia (Teesson et al., 2017).

Recently, we estimated the likelihood of successfully completing OUD within five years among a national cohort of patients (all adults admitted to public treatment services in 2008/09; N=54,357; Eastwood et al., 2017). Approximately 1:7 patients were enrolled in OST continuously up to the five-year follow-up. In the present study, we report on the status of this cohort and determine follow-up outcomes over the next two years. This is the first national outcome study of long-term, continuous OST in England. To our knowledge, there has been no national study of OST over this time-frame reported elsewhere.

In this report, we aim to:

(1) identify heroin use response trajectories during five years of OST and estimate associations with patient-level characteristics and treatment exposure;

(2) estimate whether heroin use response trajectories predict positive outcome during the sixth and seventh year of follow-up.

We hypothesised that: (a) patients with trajectories demonstrating positive response to ongoing OST would be more likely to exit treatment successfully; and (b) adjunctive psychosocial, in-patient and residential interventions would increase the likelihood of completing OST successfully.

2. Methods

2.1 Design

This was a seven-year, prospective observational cohort study of all publicly-funded specialist community-setting treatment services providing OST in England reporting to the National Drug Treatment Monitoring System (NDTMS). The study is reported following the RECORD guidelines for observational research using routinely collected health data (Benchimol et al., 2015).

The study cohort is all adults (≥18 years; n=7,877) diagnosed with OUD (almost all relating to use of heroin) who initiated treatment between 1 April 2008 and 31 March 2009, were continuously enrolled in OST for the next five years (ending 31 March 2014) and then followed-up to 30 September 2016. Following the NDTMS reporting protocol, 'continuous enrolment' was defined as either a single unbroken episode of OST, or two or more linked (continuing care) episodes in which there was no more than 21 days between the end of one methadone or buprenorphine prescribing intervention and the start of another (Public Health England, 2015).

2.2 Measures

2.2.1 Developmental trajectory indicator

The Treatment Outcomes Profile (TOP; Marsden et al., 2008) is the English national standard measure for substance use disorder treatment outcomes monitoring. The TOP is a structured clinical interview which is completed at admission, every six months thereafter, and at the completion of treatment. In this study, we used the number of days of heroin use in the 28 days prior to each TOP interview conducted between Year 1 (2008/09) and Year 5 (2013/14).

2.2.2 Outcome measure

'Successful completion' of treatment has been widely used as an outcome measure in effectiveness studies. Definitions vary, but this typically denotes satisfactory resolution of primary clinical problems and agreement between the clinician and patient to exit treatment (e.g. Luchansky et al., 2000; Alterman et al., 2001; Stahler et al., 2016).

The outcome measure in the present study combined two components: successful completion and no re-presentation (SCNR). SCNR is the English national proxy remission measure for OUD treatment outcome monitoring (Public Health England, 2015). The 'successful completion' component was measured in Year 6 and Year 7 (ending 31 March 2016). It was defined as a clinician-verified report of a patient who had completed OST, was in remission from OUD, was abstinent from heroin (and any other non-medical opioids) and cocaine, and had attained their care plan goals. The 'no re-presentation' element captures the extent to which the successful completion is sustained by linking patients with a successful completion to the community-based and prison-based treatment databases, as well as the Office for National Statistics' fatal drug-poisoning database over the subsequent six-month period (ending 30 September 2016), and removing all cases of re-presentation to treatment or fatal overdose from the summative effectiveness measure.

2.2.3 Baseline covariate measures

The following patient demographic, clinical and previous treatment exposure variables (all recorded at initial assessment) were included as potential confounders in the analysis:

Demographic. Sex; age (centred at 18 years and utilised in five-year increments); Black and Minority Ethnicities (BME: a legal monitoring requirement; *Race Relations (Amendment) Act*, 2000); employed; housing problems (defined primarily as having no fixed abode, but can also include squatting, short-term hostel/B&B, staying with friends/relatives [homeless, herein]);

Social deprivation. Local area deprivation was measured by the English Indices of Multiple Deprivation (IMD; Department for Communities and Local Government, 2007). IMD data were linked to NDTMS based on the patient's residential postcode district or the location of their first treatment provider in instances of missing postcode information.

Treatment admission drug use latent class. Four heroin-based latent classes from admission data: (1) heroin low level with concurrent drug disorder; (2) heroin, crack and alcohol; (3) heroin and crack, and (4) heroin, crack and cannabis. These classes were identified in Eastwood et al. (2017).

Injecting status. Recorded at the start of treatment, as: (1) never injected; (2) lifetime history of injecting; and (3) current injector.

Duration of heroin use 'career'. This was defined as the number of years between first initiation to heroin use and initiating OUD treatment. In the models, this variable was mean centred and utilised in five-year increments.

Treatment history. The patient's referral route into treatment was categorised as: (1) self-referred; (2) criminal-justice system; or (3) other. Whether a patient had previously accessed OUD treatment was also included.

Adjunctive treatment exposure. Together with OST, NDTMS records the following interventions: psychosocial interventions; in-patient detoxification, and residential rehabilitation.

2.3 Statistical analysis

Data management was done with SPSS (version 21). We used multilevel Latent Class Growth Analysis (LCGA) to identify discrete, non-overlapping heroin use change trajectories across five-years of OST (MPlus; version 7). Management of missing data by multiple imputation and all regression analyses was done with Stata (version 13).

2.3.1 Heroin use trajectories

In a longitudinal latent analysis of behaviour change, trajectory membership can be influenced by inclusion of covariates and distal outcomes (Huang et al., 2010). Following recommendation by Nagin

(2005), 1-class through 6-class models were fit to the data. Each model assumed a Poisson distribution and 5,000 random sets of starting values were used to guard against convergence on local maxima (McLachlan and Peel, 2000). A minimum class size of 5% was set for utility (Borders and Booth, 2012; Willey et al., 2016).

Trajectory identification was informed by posterior fit statistics. As patients were nested within different local treatment systems, we used multilevel LCGA models and an intra-class correlation coefficient (ICC) was computed for each class (Asparouhov and Muthén, 2007). Multinomial logistic regression then regressed trajectory classes on patient-level characteristics. Robust standard errors were utilised to calculate 95% confidence intervals (CI), to account for clustering of patients in each treatment system.

2.3.2 Outcome analysis

A multilevel, multivariable logistic regression model was used to estimate the likelihood of SCNR (Stata command: *meqrlogit*), and the ICC was estimated to assess intercept variation. As a sensitivity analysis, we calculated the E-value from the adjusted odds ratios of the LCGA trajectories and the estimate of its uncertainty from the CIs closest to the null. In this application, the E-value is the minimum strength needed by an unmeasured confounder to account for any significant association between trajectory membership and outcome, conditional on the included covariates (VanderWeele and Ding, 2017).

2.3.3 Missing data

LCGA is implemented by full-information maximisation likelihood and can assign patients with at least one measurement to a latent class. However, a complete case analysis may yield biased estimates due to missing covariate data. With no evidence that either the predictors or outcome variables were not missing-at-random (Little and Rubin, 1987), we created a multiply imputed dataset (Stata command: *MI impute chained*). Logistic regression, multinomial regression, and predictive mean matching were utilised, respectively, for binary, multinomial or continuous covariates with missing data. Twenty probabilistic datasets were imputed, resulting in a relative efficiency of over 98% (Rubin, 1987) and a reduction in power of less than 1% (Graham et al., 2007).

3. Results

3.1 Study cohort

Patients were recruited from all 149 local treatment systems in England (median 41; interquartile range [IQR] 23-71).

The flow of the 7,877 participants continuously enrolled in OST for five years is shown in **Figure 1**. Two percent of the cohort (n=158) had no TOP data and were removed. Therefore, LCGA was undertaken on 7,719 cases. A median of 10 TOP interviews were completed (IQR 8-11) and 2,211 patients (28.6%) completed all 11 TOP assessments. A further 58 people (0.7%) were removed as their follow-up status could not be determined.

At the end of Year 7, 4,616 (60.3%) were still enrolled in OST. During Year 6 and 7, 1,987 (25.9%) exited treatment unsuccessfully, and 1,058 (13.8%) successfully completed treatment. Among those successfully completing treatment, 16.5% (n=175) were re-admitted to community treatment in the next six months, five were incarcerated and one person died from opioid-related poisoning.

The 'successful completion and no re-presentation' (SCNR) outcome was achieved by 877 (28.8%) of those discharged from OST (n=3,045).

3.2 Heroin use during five years of OST

Heroin use was reported by 85.8% of the cohort during the 28-days before the start of treatment (**Table 1**).

Proportionately, the greatest reduction in heroin was in the first six months of OST, at which point 62.7% were still using. Overall, 39.6% of the cohort were using heroin at Year 3, and there was a slight increase at each six-monthly assessment to Year 5 (43.2%). The mean number of days used reduced from 19.5 days at intake to 7.4 days at six months and did not exceed four days after 2.5 years in treatment. Correlations over follow-up are shown in Supplementary Material (**Table S1**).

3.3 Heroin use trajectories

Table 2 displays the results of the multilevel LCGA models. Model indicators pointed to a 6-class solution. However, two classes had consistently low heroin use over the five-years. Accordingly, we judged a parsimonious 5-class model to be optimal. The ICC for classes 1, 2, 4 and 5 ranged between 0.46 and 0.49 and was 0.04 for class 3.

We labelled the heroin use trajectory classes as follows (**Figure 1**):

- Class 1 (n=1,617, 20.9%: '*gradual decreasing*')
- Class 2 (n=1,673, 21.7%: '*decreasing then increasing*')
- Class 3 (n=1,310, 17.0%: '*continued low-level*')
- Class 4 (n=1,973, 25.6%: '*rapid decreasing*')
- Class 5 (n=1,146, 14.8%: '*continued high-level*')

3.4 Patient-level characteristics

Patient-level characteristics are shown in **Table 3**, together with the results of the all-case multinomial logistic regression of the heroin use trajectory classes on patient-level characteristics. Compared to the poor response ('continued high-level') class, participants in the other classes had less previous OUD treatment exposure, and the 'decreasing then increasing', 'continued low-level' and 'rapid decreasing' classes were less likely to be currently injecting at admission.

The 'decreasing then increasing' heroin use class had more men and were less likely to be resident in an area of high social deprivation. The 'continued high-level' heroin use class were more likely to be exposed to psychosocial, in-patient and residential treatments during their enrolment in OST.

3.5 Treatment status at the end of Year 7

Continued enrolment in OST at the end of Year 7 was not associated with heroin use trajectory (**Table 4**). Among the treatment leavers, the 'continued high-level' heroin users were most likely to have an unsuccessful discharge. There was an outcome response gradient by class among those who left treatment successfully: successful completion of treatment was recorded for 8.6% of the 'continued high-level' class compared to 18.7% of the 'rapid-decreasing' class. Patients who continuously enrolled at Year 7 were removed from further analysis at this point.

Compared to the 'rapid decreasing' heroin use class (re-admission rate 11.2%), re-presentation within six months for community treatment was more likely among the 'continued high-level' heroin use class (22.4%; odds ratio [OR] 2.29; 95% CI 1.29-4.08); followed by the 'decreasing then increasing' class (22.2%; OR 2.26; 95% CI 1.38-3.71), the 'gradual decreasing' class (17.3%; OR 1.72; 95% CI 1.08-2.73) and the 'continued low-level' class (17.8%; OR 1.66; 95% CI 1.01-2.72).

3.5 Impact of trajectory membership on outcome

The poor responding 'continued high-level' heroin using class had the lowest proportion achieving SCNR (16.2%), followed by the 'decreasing then increasing' group (19.6%). The 'continued low-level use' and 'gradual decreasing use' groups has similar levels of SCNR (31.2% and 31.7%, respectively), while SCNR was most likely to be attained by the 'rapid decreasing' class (39.7%).

The multiply imputed, multilevel logistic regression analysis (**Table 5**) indicated that three trajectory groups (i.e. *'gradual decreasing', 'continued low-level' and 'rapid decreasing')* were more likely to achieve SCNR compared to the 'continued high-level' class (adjusted odds ratio [AOR] 2.40 [95% CI 1.77 to 3.26]); AOR 2.46 [95% CI 1.78 to 3.40]; AOR 3.26 [95% CI 2.43 to 4.37]), respectively.

The E-value estimate for the 'gradual decreasing use' class was 4.23 (with an uncertainty estimate of 2.94 for the minimum risk ratio needed to shift the CI to the null), E=4.36 (uncertainty estimate = 2.96) for the 'continued low-level use' class and E=5.97 (uncertainty estimate = 4.29) for the 'rapid decreasing use' class. There was also an increased likelihood of achieving SCNR among those with pre-admission employment (AOR 1.45; 95% CI 1.15 to 1.83), those who received adjunctive psychosocial treatment during OST (AOR 1.44; 95% CI 1.03 to 2.02) and a positive association for increasing age (AOR 1.07; 95% CI 1.00 to 2.14). Longer heroin using career, lifetime history of injecting, and referral from the criminal justice system was associated with a decreased likelihood of achieving SCNR.

3.5 Post-hoc analysis

Finally, we created a binary 'non-response' measure by combining the 'continued high-level use' and 'decreasing then increasing use' trajectory groups against the remaining three trajectory groups. This measure was then collapsed at the local treatment system level, resulting in a range of non-response from 0-70%. Also available at local area level were the prevalence of opiate users per 1,000 population in 2008/09 (Hay et al., 2010), the rate of offending per 1,000 population (Office for National Statistics,

2016), and the rate of drug-related deaths per million population (Public Health England, 2016). Non-response was regressed on these three measures in a linear regression. The offending rate and the drug-related death rate was not associated with non-response. However, for every extra opiate user per 1,000 population, there was an increase in non-response by almost two percentage points (1.97; 95% CI 0.76 to 3.17).

4. Discussion

In a time of increased focus on recovery (HM Government, 2017; Laudet and Humphreys, 2013), a greater understanding of the heterogeneous response to treatment is required by policy makers, treatment purchasers and clinicians to inform their decision making processes. This report extends our previous study (Eastwood et al., 2017) by estimating heroin use change trajectories over long-term enrolment in OST. We identified five heroin use trajectory groups and found that the trajectory groups tending towards abstinence at Year 5 were significantly more likely to achieve a sustained benefit from treatment (SCNR follow-up outcome).

4.1 Integration with the literature

In the treatment literature, several demographic and patient-level characteristics have been linked to developmental trajectories associated with relatively poor treatment response, including: males; people from some ethnic minorities; lower educational achievement; earlier onset of drug use, and involvement with the criminal justice system (Grella and Lovinger, 2011; Hser et al., 2008, 2007).

Our ‘continued low-level’, ‘continued high-level’ and ‘decreasing then increasing’ classes are similar to the ‘low use’, ‘high use’ and ‘increasing use’ response groups identified by Hser’s group (Hser et al., 2008). Other studies have also highlighted a sub-population that does not exhibit substantial reduction in drug use, as well as a group demonstrating rapid reductions (Grella and Lovinger, 2011; Teesson et al., 2017). This points to a degree of phenotypic similarity across different countries, settings and cohort characteristics. Similar to the Australian study (Teesson et al., 2017), we note that few baseline covariates predict trajectory membership, although higher deprivation, currently injecting, and previous treatment were associated with relative non-response to treatment.

The validity of person-centred latent trajectory modelling has been criticised (Sher et al., 2011). Our finding that more favourable trajectory memberships are associated with sustained benefit provides support for the predictive validity of the approach. It also extends previous work documenting associations with decreased mortality and better employment, substance use and mental health outcomes (Hser et al., 2007; Teesson et al., 2017; Hser et al., 2017), and highlights the importance of incorporating independent outcomes in person-centred research design.

Our findings also highlight the positive role of employment in recovery, although it is interesting that stable housing did not affect the likelihood of recovery as in other studies (e.g. Cloud and Granfield, 2008). Injecting and criminal justice referrals were, as expected (Marsden et al., 2012), negatively associated with positive outcome.

4.2 Clinical implications

In our study, we estimate that one in seven patients demonstrate sustained non-response over significant periods of time and a further fifth of patients exhibit a tendency to deteriorate after three years of treatment. Continued illicit opioid use on top of an opioid prescription is a recognised problem (Clinical Guidelines on Drug Misuse and Dependence Update 2017 Independent Expert Working Group, 2017). It is important for clinicians to identify non-response at an early stage and to review and optimise the treatment care package. Several clinical responses are available, including: increasing the dose; dividing the dose into smaller daily doses in the case of faster metabolism; offering to change the OST medication, and reintroducing daily supervised consumption (ibid). Service user views on medication should be taken into account, as a quarter consider the OST dose to be 'poor or bad' (Advisory Council on the Misuse of Drugs, 2015). In the US, around a quarter of patients also receive methadone doses too low to be effective (D'Aunno et al., 2014).

4.3 Policy implications

Our finding that more than 40% of patients continue to use illicit opioids after five years of continuous treatment supports the conclusion that a blanket time limit on prescribing would not be clinically appropriate (Advisory Council on the Misuse of Drugs, 2014). National drug treatment administrators should make available performance monitoring reports for clinics and treatment purchasers focused on long-term use of illicit opioids, which could aid local planning, resource allocation and improve outcomes. Further, incorporation of prescription dose into the NDTMS would help estimate whether, and to what degree, sub-optimal dosing is associated with continued use on top.

Our finding that psychosocial interventions, received by most but not all patients, is advantageous for sustaining recovery underscores the importance of comprehensive interventions being made available in the treatment of OUD. More frequent or personalised psychosocial interventions may also be of benefit (Marsden et al., 2017). Treatment clinics may benefit from an audit of clinical practices as it has been suggested that interventions are 'front-loaded' and less intensive support is available to those in treatment over longer periods (Finch, 2003).

In the current study, it appears that areas with a greater degree of non-response are also affected by a larger opiate-using population. Although we are unable to determine a precise mechanism, there may be social network influences in operation to explain this association. For example, heroin users who have achieved abstinence often cite moving away from drug-using social networks as a factor in their success (Best et al., 2008). Greater integration of treatment services with local recovery groups may help mitigate this influence.

4.4 Strengths and limitations

A major study strength is the national, large-scale, long-term follow-up of all individuals accessing treatment for opioid use disorder in England. In addition, the consent model supporting NDTMS enables

cross-referencing with subsequent treatment admissions and drug-poisoning databases, providing the utility to examine an objective summative measure of sustained recovery from OUD.

Several limitations are also acknowledged: first, while all available covariates in NDTMS were screened in the present analysis, other covariates could further elucidate the likelihood of sustaining recovery, including treatment motivation (Simpson and Joe, 1993), engagement (Simpson et al., 1995) and other recovery strengths (Gossop et al., 2002). Second, it is possible that other interventions, such as attending Narcotics Anonymous, were experienced by the patients in this cohort. These interventions are not, however, captured by NDTMS and it is not possible to assess the potential impact these may have had. We note that the E-value parameter suggests such a variable would need to have an adjusted odds ratio of at least 2.9 to mitigate the association between trajectory membership and outcome.

4.5 Conclusions

This study highlights the importance of research analytical methods that capture longitudinal trajectories. Within a cohort of patients continuously enrolled in treatment for five years, diverse treatment-response trajectories emerge. The differential association between trajectory membership and subsequent outcomes has real application and could be important to clinicians and treatment purchasers as it indicates a substantial proportion of patients exhibit chronic or relapsing opioid use in response to treatment and may require more intensive interventions over a longer period.

Figure 1. Study profile

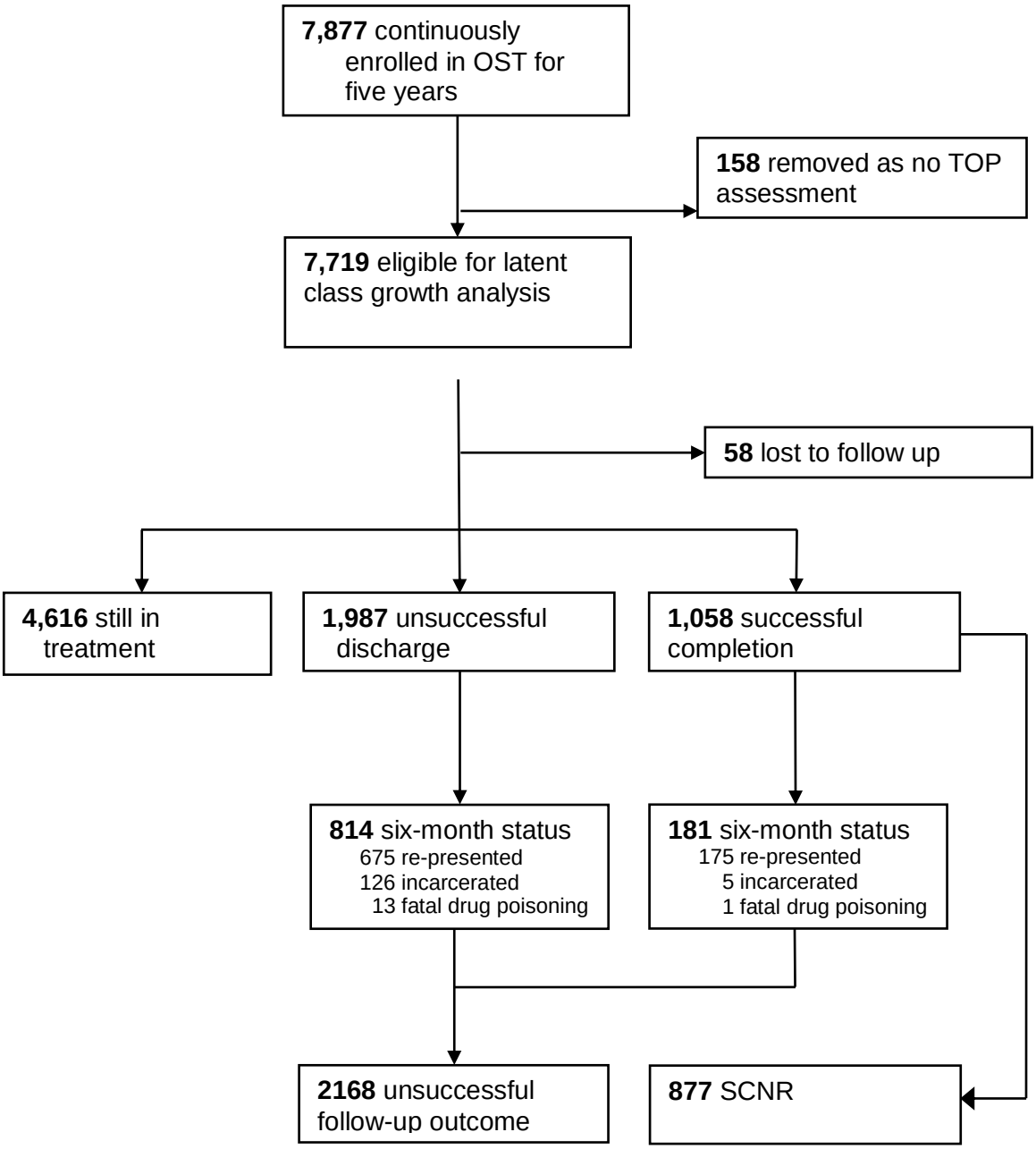

Figure 2. Heroin use trajectories over 5 years of continuous OST

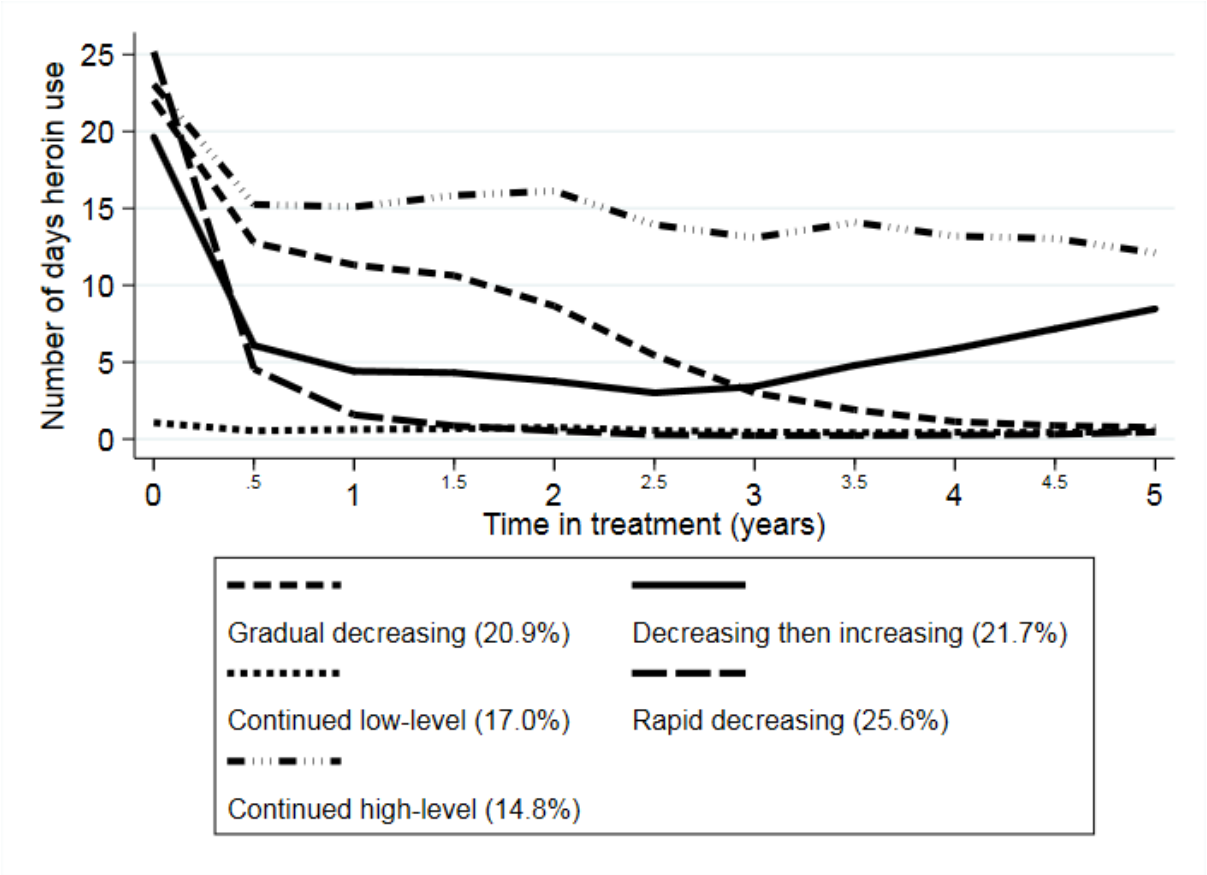

Table 1. Heroin use during five years of continuous OST (n=7,719)

TOP assessment	Responses (n)	No. (%) using heroin	Mean days used (SD) *
Admission	5,567	4,775 (85.8)	19.5 (11.6)
Year 0.5	5,774	3,622 (62.7)	7.4 (9.7)
Year 1	6,409	3,796 (59.2)	6.0 (8.7)
Year 1.5	6,449	3,673 (57.0)	5.9 (8.6)
Year 2	6,567	3,498 (53.3)	5.4 (8.3)
Year 2.5	6,649	2,899 (43.6)	4.0 (7.5)
Year 3	6,670	2,639 (39.6)	3.5 (6.9)
Year 3.5	6,713	2,729 (40.7)	3.7 (7.1)
Year 4	6,733	2,821 (41.9)	3.6 (730)
Year 4.5	6,743	2,873 (42.6)	3.9 (7.2)
Year 5	6,748	2,913 (43.2)	4.0 (7.4)

TOP = Treatment Outcomes Profile;
SD = standard deviation
* Mean days of opioid use in past 28 days.

Table 2 Unconditional multilevel latent class growth analysis of heroin use over five years (n=7,719)

	1-Class	2-Class	3-Class	4-Class	5-Class	6-Class
AIC	886002.87	671087.82	610578.39	580090.68	553248.75	537428.48
BIC	886023.73	671136.50	610654.88	580194.97	553380.86	537588.40
aBIC	886014.20	671114.25	610619.92	580147.31	553320.48	537515.31
Entropy	-	0.975	0.971	0.964	0.950	0.956
Class (probability)						
Class 1	1.00 (1.00)	0.58 (0.99)	0.42 (0.99)	0.24 (0.97)	0.21 (0.97)	0.12 (0.96)
Class 2	-	0.42 (0.99)	0.21 (0.99)	0.37 (0.99)	0.22 (0.97)	0.25 (0.97)
Class 3	-	-	0.37 (0.99)	0.23 (0.97)	0.17 (0.97)	0.18 (0.97)
Class 4	-	-	-	0.16 (0.99)	0.26 (0.94)	0.14 (0.98)
Class 5	-	-	-	-	0.15 (0.98)	0.17 (0.96)
Class 6	-	-	-	-	-	0.15 (0.95)
VLMR	-	<0.01	0.12	<0.01	<0.01	<0.01
BLRT	-	<0.01	<0.01	<0.01	<0.01	<0.01

AIC: Akaike Information Criterion;
BIC: Bayesian Information Criterion;
aBIC: sample-size adjusted BIC;
VLMR: Vuong-Lo-Mendel-Ruben test;
BLRT: bootstrapped likelihood ratio test.

Table S1. Correlation matrix of illicit opioid responses across the five-year observation period

	Admission	**Year 0.5**	**Year 1**	**Year 1.5**	**Year 2**	**Year 2.5**	**Year 3**	**Year 3.5**	**Year 4**	**Year 4.5**	**Year 5**
Admission	1.000										
Year 0.5	0.191	1.000									
Year 1	0.166	0.443	1.000								
Year 1.5	0.123	0.370	0.510	1.000							
Year 2	0.125	0.305	0.382	0.491	1.000						
Year 2.5	0.099	0.261	0.300	0.375	0.478	1.000					
Year 3	0.103	0.235	0.291	0.346	0.372	0.429	1.000				
Year 3.5	0.100	0.214	0.280	0.326	0.369	0.390	0.483	1.000			
Year 4	0.098	0.214	0.262	0.297	0.331	0.333	0.409	0.515	1.000		
Year 4.5	0.104	0.197	0.234	0.263	0.319	0.327	0.347	0.433	0.514	1.000	
Year 5	0.069	0.173	0.215	0.262	0.293	0.283	0.305	0.352	0.422	0.502	1.000

All correlations in the matrix statistically significant at 99% error level (Bonferroni corrected).

Table 3. Patient-level characteristics by heroin use trajectories (n=7,719)

Covariate	Total	Continued high-level (n=1,146)	Decreasing then increasing (n=1,673)	Continued low-level (n=1,310)	Gradual decreasing (n=1,617)	Rapid decreasing (n=1,973)
Male	5,562 (72.1)	(72.2)	**(75.2)**	(72.7)	(70.5)	(70.1)
Age [a]	34.4 (7.9)	34.2 (7.4)	33.9 (7.5)	35.2 (8.3)	33.7 (7.8)	34.9 (8.2)
Black/Minority Ethnic	718 (9.3)	(8.4)	(9.7)	(8.5)	(8.7)	(10.5)
Employed [b]	1,164 (15.7)	(13.7)	(16.9)	(13.3)	(14.1)	(18.5)
Homeless [c]	1,775 (23.4)	(25.4)	(23.7)	(20.6)	(26.1)	(21.5)
Social deprivation:						
Quintile 1 (lowest)	1,935 (25.1)	(23.6)	(25.5)	(25.9)	(25.2)	(24.9)
Quintile 2	1,562 (20.2)	(19.0)	(20.1)	(18.9)	(18.6)	(23.3)
Quintile 3	1,434 (18.6)	(18.1)	(19.4)	(18.2)	(19.2)	(17.9)
Quintile 4	1,595 (20.7)	(20.9)	(21.2)	(20.0)	(21.3)	(20.1)
Quintile 5 (highest)	1,193 (15.5)	(18.5)	**(13.8)**	(17.0)	(15.7)	**(13.8)**
Heroin career [a,d]	12.3 (7.7)	12.3 (7.2)	11.9 (7.2)	13.3 (8.0)	11.9 (7.4)	12.5 (8.2)
Drug injecting: [e]						
Never	2,290 (29.9)	(25.4)	(31.5)	(27.7)	(27.9)	(34.3)
Lifetime	2,976 (38.9)	(33.3)	(36.6)	**(54.5)**	(35.7)	(36.5)
Current	2,387 (31.2)	(41.3)	**(31.9)**	**(17.8)**	(36.4)	**(29.2)**
Referral source:						
Other	2,964 (38.4)	(32.6)	(37.2)	(49.5)	(36.2)	(37.2)
Self	3,244 (42.0)	(46.3)	(44.3)	**(26.8)**	(43.5)	(46.6)
Criminal justice	1,511 (19.6)	(21.2)	(18.5)	(23.7)	(20.3)	(16.2)
Previous OUD treatment	4,871 (63.1)	(72.8)	**(64.4)**	**(59.4)**	**(65.9)**	**(56.6)**
Drug use sub-population:						
Heroin low-level concurrent drug use disorder	4,295 (55.6)	(55.2)	(56.6)	(53.4)	(54.9)	(57.1)
Heroin, crack and alcohol	388 (5.0)	(4.9)	(5.1)	(4.6)	(6.3)	(4.3)
Heroin and crack	2,589 (33.5)	(34.8)	(32.6)	(36.0)	(32.8)	(32.5)
Heroin, crack and cannabis	447 (5.8)	(5.1)	(5.7)	(6.0)	(5.9)	(6.1)
Adjunctive treatment exposure:						
Psychosocial	7,121 (92.3)	(95.0)	(93.0)	**(90.5)**	(93.9)	**(89.8)**
In-patient	566 (7.3)	(11.4)	**(7.2)**	**(5.3)**	(8.8)	**(5.2)**
Residential	109 (1.4)	(3.0)	(1.9)	(0.9)	**(1.2)**	**(0.6)**

Figures in parentheses in table are number of participants (percentages) unless otherwise stated.
Emboldened percentages and means are statistically significant (P<0.05) from all-case, multiply imputed, multivariable multinomial logistic regression (continued high-level use group as referent).
a Year (SD);
b Percentage after excluding 286 participants with missing data on this covariate;
c Percentage after excluding 123 participants missing data on this covariate;
d Percentage after excluding 261 participants missing data on this covariate; e Percentage after excluding 66 participants missing data on this covariate

Table 4. OST status at Year 7, by heroin use trajectory (n = 7,661)

Heroin use trajectory class	Still enrolled	Unsuccessful discharge	Successful completion
Continued high-level (n=1,142)	678 (59.4)	366 (32.1)	98 (8.6)
Decreasing then increasing (n=1,660)	1,016 (61.2)	482 (29.0)	162 (9.8)
Continued low-level (n=1,298)	803 (61.9)	304 (23.4)	191 (14.7)
Gradual decreasing (n=1,604)	975 (60.8)	388 (24.2)	241 (15.0)
Rapid decreasing (n=1,957)	1,144 (58.5)	447 (22.8)	366 (18.7)
Total	**4,616 (60.3)**	**1,987 (25.9)**	**1,058 (13.8)**

Numbers in parentheses are percentages unless otherwise shown

Table 5. Unadjusted and multi-level, all-case multivariable logistic regression of SCNR outcome (n=3,045)

Covariate	Unadjusted OR (95% CI)	All-case AOR (95% CI)
Male	0.90 (0.75, 1.07)	0.95 (0.79, 1.15)
Age	1.03 (0.98, 1.08)	**1.07 (1.00, 1.14)**
Black/Minority Ethnic	1.03 (0.78, 1.36)	0.94 (0.70, 1.26)
Employed	**1.61 (1.29, 1.99)**	**1.45 (1.15, 1.83)**
Homeless	**0.79 (0.66, 0.96)**	0.88 (0.72, 1.08)
Social deprivation		
Quintile 1 (lowest)	1.06 (0.84, 1.35)	1.07 (0.83, 1.37)
Quintile 2	0.78 (0.60, 1.00)	0.84 (0.64, 1.09)
Quintile 3	0.86 (0.67, 1.10)	0.94 (0.73, 1.22)
Quintile 4	0.82 (0.62, 1.09)	0.89 (0.67, 1.20)
Quintile 5 (highest)	-	-
Heroin career	0.95 (0.90, 1.01)	**0.93 (0.87, 1.00)**
Drug injecting:		
Never	-	-
Lifetime	**0.71 (0.58, 0.86)**	**0.79 (0.64, 0.97)**
Current	**0.65 (0.53, 0.80)**	0.80 (0.64, 1.00)
Referral source:		
Other	-	-
Self	0.92 (0.77, 1.10)	0.94 (0.78, 1.14)
Criminal justice	**0.62 (0.50, 0.79)**	**0.68 (0.54, 0.87)**
Previous OUD treatment	**0.73 (0.62, 0.86)**	0.87 (0.73, 1.03)
Drug use classification:		
Heroin low level concurrent drug disorder	-	-
Heroin, crack and alcohol	1.05 (0.72, 1.54)	1.02 (0.69, 1.51)
Heroin and crack	1.01 (0.85, 1.20)	0.99 (0.83, 1.19)
Heroin, crack and cannabis	0.93 (0.65, 1.33)	0.87 (0.60, 1.25)
Treatment exposure:		
Psychosocial	1.26 (0.91, 1.75)	**1.44 (1.03, 2.02)**
In-patient	**0.70 (0.52, 0.95)**	0.79 (0.57, 1.11)
Residential	0.84 (0.43, 1.64)	1.34 (0.65, 2.76)
Heroin use trajectory class:		
Gradual decreasing	**2.37 (1.75, 3.21)**	**2.40 (1.77, 3.26)**
Decreasing then increasing	1.28 (0.93, 1.76)	1.23 (0.89, 1.70)
Continued low-level	**2.48 (1.81, 3.40)**	**2.46 (1.78, 3.40)**
Rapid decreasing	**3.47 (2.60, 4.64)**	**3.26 (2.43, 4.37)**
Continued high-level	-	-
Model statistics		
Constant	-	0.16 (0.09, 0.29)
Wald $\chi 2$ (d.f. = 25)	-	159.6 - 163.8
LR test $\chi 2$ (d.f. = 1)	-	12.0 - 12.7
Intra-class correlation	-	0.03 - 0.03

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